"FORMULATION AND IN-VITRO EVALUATION OF GABAPENTIN ORAL CONTROLLED RELEASE MATRIX TABLETS"

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In Partial fulfillment of the requirements for the award of the Degree of

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LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CERTIFICATE

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Constitutes the original work carried out by

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EVALUATION CERTIFICATE

This is to certify that this dissertation entitled **Formulation and Evaluation of Gabapentin oral controlled release matrix tablets** constitutes the original work carried out by **Mr.K.GOVINDASAMY,** under the guidance and supervision of **Dr.R.P.EZHIL MUTHU M.PHARM., Ph.D.,** Head of the department, Department of pharmaceutics, Padmavathi college of pharmacy & Reasearch Institute, Periyanahalli, 635205 Dharmapuri has been evaluated on -

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Evaluaters:

1. **2.**

INTRODUCTION

1. INTRODUCTION

In recent years, considerable attention has been focused on the development of new drug delivery systems. There are a number of reasons for the intense interest in new systems. First, recognition of the possibility of repatenting successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with the increasing expense in bringing new drug entities to market, has encouraged the development of new drug delivery systems. Second, new systems are needed to deliver the novel, genetically engineered pharmaceuticals, i.e., the proteins and peptides, to their site of action without incurring significant immunogenicity or biological inactivation. Third, treating enzyme deficient diseases and cancer therapies can be improved by better targeting. Finally, therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body, thereby reducing both size and number of doses.[1]

ADVANTAGES OF CONVENTIONAL DOSAGE FORMS:

- This is the oldest and commonest mode of drug administration. It is safer and more convenient than the other mode of drug administration.
- This mode of drug administration does not need assistance and non-invasive in nature.
- As mode of administration is non-invasive in nature, so no need the competent medical personnel for drug administration.
- Inflammation and pain associated with parenteral administration should be avoided.
- The medicament or the dosage forms need not to be sterile for oral administration.

- As it is non-sterile in nature, so it is cheapest when compared with other dosage forms.

DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS:

- Action is slower and thus not suitable for emergencies.
- Unpalatable drugs are difficult to administer.
- May cause nausea and vomiting.
- This route of administration cannot be used for uncooperative, unconscious and vomiting patients.
- Certain drugs are not absorbed from oral route. (E.g. streptomycin)
- Some drugs are inactivated by gastric juice (E.g. penicillin G, Insulin) or in liver (E.g. nitroglycerine, testosterone and lidocaine) cannot be administered by oral route.

1.1 ORAL DRUG DELIVERY [2, 3]

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the Minimum Effective Plasma Concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized:

1. ***Extended-release drug products*****.** A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

2. ***Delayed-release drug products*****.** A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. ***Targeted-release drug products*****.** A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

Modified-release drug products are designed for different routes of administration based on the physiochemical, pharmacologic and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form. Several different terms are now defined to describe

the available types of modified-release drug products based on the drug release characteristics of the products.

1.2 ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS[2,3]

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled Release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

1.2.1 Advantages of Controlled Drug Delivery Systems:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects.
- Minimize drug accumulation with chronic dosing.
- Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
- Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.

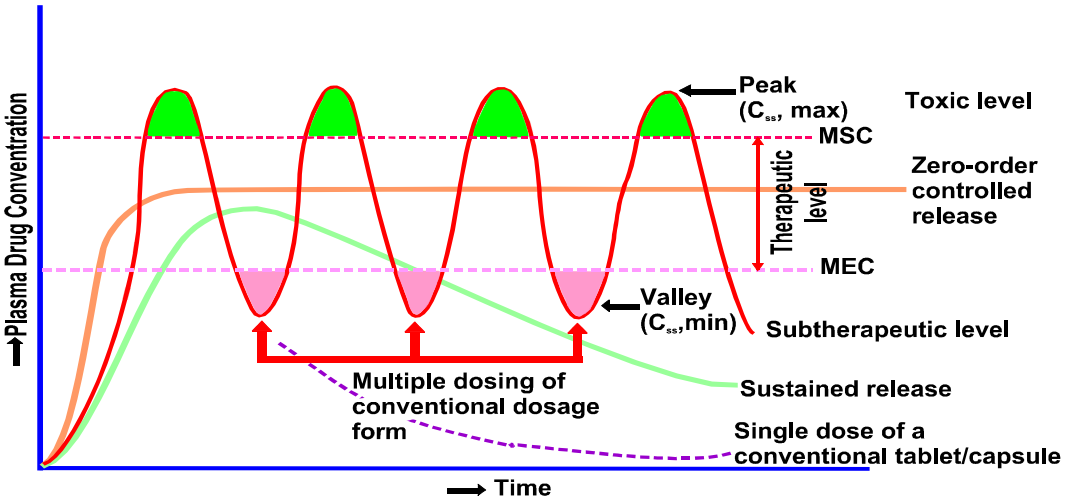
1.2.2 Disadvantages of Controlled Drug Delivery Systems:

- Increased variability among dosage units.
- Poor in vitro – in vivo correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.

- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counseling.

Figure No.1

A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = Maximum Safe Concentration, MEC = Minimum Effective Concentration)



1.3 SELECTION OF DRUG CANDIDATE FOR CONTROLLED RELEASE DOSAGE FORMS[4]

The physico - chemical properties of the drug such as pKa, partition coefficient, biological half life, molecular weight, dose of the drug etc., have to be considered before selection.

Characteristics of drugs suitable for formulation as Sustained Release Products

- Exhibit moderate rates of absorption and excretion.
- Uniform absorption throughout the gastrointestinal tract.

- Administered in relatively small doses.
- Possess good margin of safety.
- Used for treatment of chronic therapy.

Characteristics of drugs unsuitable for formulation as Sustained Release Products

- Not effectively absorbed in the lower intestine (Riboflavin).
- Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Frusemide).
- Long biological half lives greater than 12 hours (Diazepam, Phenytoin).
- Large doses required, 1gm (Sulphonamides)
- Drugs with low therapeutic index (Phenobarbital, Digoxin).
- Precise dosage titrated to individuals required (anticoagulants)
- No clear advantage for sustained release formulation (griseofulvin)

1.4 FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF CONTROLLED RELEASE PRODUCTS[4]

The design of controlled - release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance.

1. Physicochemical factors

a. Aqueous solubility
b. Partition coefficient
c. Drug stability
d. Protein binding
e. Molecular size and Diffusivity

2. Biological factors

a) Absorption

b) Distribution
c) Elimination
d) Biological half life and Duration of action
e) Side effects and Margin of safety
f) Dose size
g) Disease state

1.4.1 PHYSICOCHEMICAL FACTORS[4]

a. Aqueous solubility:

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membrane. The choice of mechanism for oral sustained release systems is limited by aqueous solubility of the drug. Diffusion systems will be poor choices for slightly soluble drugs since the driving force for diffusion; the concentration in aqueous solution will be low. Such drugs may be effectively incorporated in matrix system.

Partition coefficient:

Partition coefficient ($K_{o/w}$) is defined as the ratio of the fraction of the drug in an oil phase to that of an adjacent aqueous phase.

$$K=C_0/C_w$$

Where,

C_0 = Equilibrium concentration of all forms of the drug e.g. ionized and unionized in an organic phase at equilibrium

C_w = Equilibrium concentration of all forms in aqueous phase

Accordingly, compounds with a relatively high $K_{o/w}$ are predominantly lipid-soluble and consequently, have very low aqueous solubility. Furthermore, these compounds can usually persist in the body for long periods as they can localize in the lipid membranes of cells. (e.g.: Phenothiazines). Compounds with very low $K_{o/w}$ will have difficulty in penetrating membranes, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on partitioning characteristics of the drug. Drugs with a partition coefficient that is higher or lower than the optimum (i.e., 1000/1) in general, are poor candidates for formulation into Controlled Release dosage forms.

b. Drug stability:

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. For drugs like Propanthline that are unstable in the stomach, the most appropriate controlling unit would be the one that releases its contents only in the intestine. The reverse in the case for drugs like Propanthline that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach. In general, drugs with significant stability problems in any particular area of the gastrointestinal tract are less suitable for formulation into controlled release systems.

c. Protein binding:

Many drugs bind to plasma proteins with a significant influence on the duration of drug action. If a drug has binding properties

with a particular protein, then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a controlled release dosage form.

d. Molecular size and Diffusivity:

Drugs in most of the sustained release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through these membranes is known as diffusivity (diffusion coefficient). This diffusivity is a function of its molecular size (or molecular weight) and is related by the equation.

$$\text{Log } D = S_v \log_V + K_v = S_m \log M + K_m$$

Where,

D = Diffusivity

M = Molecular weight

V = Molecular volume

S_v, S_m, K_v and K_m = Constants in a particular system.

In general the denser the medium, the smaller is the diffusivity.

1.4.2 BIOLOGICAL FACTORS[4]

The design of sustained release products should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing.

i. Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considering it's formulation into a sustained release dosage form. To maintain a constant blood or tissue level of drug, it must be uniformly released from the sustained release system and then uniformly absorbed. Since the rate-limiting step in drug delivery from a controlled release product is its release from a dosage form, a rapid rate of absorption of drug relative to its release is essential if the system is to be successful. In case of sustained release dosage form, the rate constant for drug release is much less than the constant for drug absorption (i.e., $K_r <<< K_a$). Assuming that the transit time of a drug through the absorption area of the gastro intestinal tract is between 9 and 12 hrs, the maximum absorption half-life should be 3 to 4 hrs.

This corresponds to a minimum absorption rate constant K_a of 0.17 to 0.23 hr^{-1} necessary for about 80 to 95 % absorption over a 9 to 12 hr transit time. For a drug with a very rapid rate of absorption (i.e., $K_a >> 0.23$ hr^{-1}), the above discussion implies that a first order release rate constant $K_r <$ 0.17 hr^{-1} is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release dosage forms.

ii. Distribution:

Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution (V_d) and the ratio of drug concentration in the tissue to that in plasma (T/P ratio) at the steady state. In general, the bound portion of drug can be considered inactive and unable to cross membranes. At high binding one sees prolonged drug action. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. The total apparent volume of distribution for a drug at steady state can be calculated from the following equation.

$$V_{dss} = [(k_{12}+k_{21})/k_{21}]V_p$$

Where,

V_{dss} is the apparent volume of distribution at steady state.

K_{12} and K_{21} are the constants for the distribution of drug from the central to peripheral compartment and from peripheral to central compartments respectively.

V_p is the volume of central compartment.

iii. Elimination:

Elimination of a drug involves two aspects i.e., metabolism and excretion. Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active metabolite. Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability particularly from slowly releasing dosage forms. Metabolism of a drug will be reflected in the elimination rate constant

of a drug or by the appearance of a metabolite. It is possible to incorporate this pharmacokinetic property into the design of controlled release product, provided that the rate and extent of metabolism are predictable and that the rate constant(s) for the process are not too large. Undoubtedly, complex metabolic patterns would make the design much more difficult, particularly when biological activity is wholly or partly due to a metabolite, as is the case of Isosorbide 2,5-dinitrate.

iv. Biological half life and Duration of action:

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. The biological half-life and hence duration of action of a drug obviously play a major role in the process of considering a drug for sustained release. Therapeutic compounds with a short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half life as it may require excessively large amounts of drug in each dosage unit to maintain controlled effect.

In general, drugs with half-life shorter than two hours are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already controlled.

v. Side effects and Margin of safety:

Theoretically, the incidence of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time, and hence controlled release formulations appear

to offer a solution to this problem. By slowing the rate at which the drugs are released, the chances of gastrointestinal irritation will be reduced due to a smaller amount of drug exposed to the gastrointestinal mucosa at the given time. The most widely used measure of the margin of safety of a drug is its Therapeutic Index (TI).

$$TI = TD50/ED50$$

Where,

TD_{50} = Median toxic dose

ED_{50} = Median effective dose

Drugs with very small value of therapeutic index usually are poor candidates as controlled release products.

vi. Dose Size:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum for conventional dosage form. This also holds for controlled release dosage forms.

Vii. Disease State:

Sometimes the disease states are considered before the designing of an oral controlled release dosage form. This can be explained by taking the example of Aspirin (for rheumatic arthritis) which is not a suitable candidate for sustained release dosage form. Still an aspirin sustained release dosage from could be advantageous to maintain therapeutic concentrations, particularly through out the night, thus alleviating morning stiffness.

1.5 TYPES OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS[2, 3, 4]

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

A. Dissolution controlled release systems
B. Diffusion controlled release systems
C. Diffusion and dissolution systems
D. Osmotically controlled release systems
E. Gastro retentive drug delivery systems
F. Electrically stimulated release devices
G. Ion-exchange resins

A) DISSOLUTION CONTROLLED RELEASE SYSTEMS[5]

A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate-limiting step is dissolution. This being true, sustained release preparation of drugs could be made by decreasing their rate of dissolution.

Dissolution controlled systems can be made either by

- Varying concentration of rate controlling coats or polymers (Matrix Dissolution Systems) or
- By administering the drug as a group of beads that have coating of different thickness (Encapsulated Dissolution Systems)

- Matrix Dissolution Systems are prepared by compressing the tablet with a slowly soluble polymer carrier into tablet form. Wax matrices are prepared either by congealing or dispersion the drug - wax mixture in water.

Table No.1

Dissolution controlled release system(matrix)

Commercially available products belonging to this category are given below:

Product	Active ingredient	Manufacturer
Dimetane Extentabs	Brompheniramine maleate	Robins
Quinidex Extentabs	Quinidine sulfate	Robins

Encapsulated Dissolution Systems contain beads that have different coating thickness, their release will occur in a progressive manner. Those with the thinnest layer will provide the initial dose and the maintenance of drug levels at later times will be achieved from those with thicker coating. This dissolution process at steady state is described by the Noyes-Whitney equation.

$$\frac{dc}{dt} = KDA(C_s - C) = \frac{D}{h}A(C_s - C)$$

Where,

dc/dt = dissolution rate.

K_D = Dissolution rate constant.

D = Diffusion coefficient.

C_s = Saturation solubility of the solid.

C = Concentration of solute in the bulk solution

Table No.2

Dissolution controlled release system(encapsulated)

Commercially available products belonging to this category are given below:

Product	Active ingredient	Manufacturer
Diamox Sequels	Acetazolamide	Lederle
Nicobid Temples	Nicotinic acid	Rorer

B) DIFFUSION CONTROLLED RELEASE SYSTEMS[5]

In these systems the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices.

RESERVOIR DEVICES:

Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug.

The methods used to develop reservoir type devices include micro-encapsulation of drug particles and coating of tablets containing drug cores.

Advantages:

- These devices can offer zero-order release of the drug.

Disadvantages:

- System must be physically removed from implant sites.
- Difficult to deliver high molecular weight compounds.

Table No.3

Diffusion controlled release system (reservior)

Commercially available products belonging to this category are given below:

Product	Active ingredient	Manufacturer
Nico-400	Nicotinic acid	Jones
Nitrospan	Nitroglycerin	Rorer

MATRIX DEVICES:

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. The most common method of preparation is to mix the drug with the matrix material and then compress the mixture. The drug release from a porous or granular matrix can be described by

$$M = (D_s.C_a.\{P/T\}.[2C_0-PC_a]t)^{1/2}$$

Where,

P = Porosity of the matrix

T = Tortuosity

C_a= Solubility of the drug in the release medium

D_s= Diffusion coefficient in the release medium

Advantages:

- Can deliver high molecular weight compounds.

Disadvantages:

- Cannot obtain zero order release
- Removal of remaining matrix is necessary for implanted systems

Table No.4

Diffusion controlled release system (matrix)

Commercially available products belonging to this category are given below:

Product	Active ingredient	Manufacturer
Fero-Gradumet	Ferrous sulfate	Abbott
Choledyl SA	Oxtriphylline	Parke-Davis

C) DIFFUSION AND DISSOLUTION CONTROLLED SYSTEMS[6]

In these systems the release rate of drug is determined by both the diffusion and dissolution mechanisms.

D) OSMOTICALLY CONTROLLED RELEASE SYSTEMS[3]

The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an osmotically controlled device that promotes a constant amount of water into the system, either by dissolving and releasing a constant amount of drug per unit time or by the use of a "push–pull" system that pushes the drug out at a constant rate as water flows into an expandable osmotic compartment. Drug is released via a single laser-drilled hole in the tablet.

A representative osmotic oral drug product is the "push–pull" system called Gastrointestinal Therapeutic System (GITS), developed by Alza Corporation for nifedipine (Procardia XL) and other drugs. The system consists of a semipermeable membrane and a two-layer core of osmotic ingredient and active drug. As water enters the system, the osmotic pressure builds up from the inner layer, pushing the drug out through a laser-drilled orifice in the drug layer.

E) GASTRORETENTIVE DRUG DELIVERY SYSTEMS[6]

Dosage forms that can be retained in stomach are called Gastro retentive Drug Delivery Systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

The approaches that have been pursued to increase the retention of an oral dosage form in the stomach include Bioadhesive systems, swelling and expanding systems, High density systems and Low density (Floating) systems.

1. Bioadhesive systems:

Bioadhesion is the process whereby synthetic and natural macromolecules adhere to the biological membranes in the body and remain there for an extended period of time. If the membrane substrate is mucosal layer then the process is referred to as mucoadhesion. The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.

2. Swelling and Expanding Systems

These systems increase the residence time of the dosage form in the stomach. Particles greater than 10mm are unable to enter the duodenum and are retained in the stomach. The swelling systems incorporate hydrogels which are polymers that can swell up to 100 times their dry weight. The hydrogels used must be biodegradable.

3. High density systems

In High density systems the bulk density of the dosage form must exceed that of normal stomach and should be at least 1.40. In preparing such formulations, drug can be coated on a core with heavy, inert materials such as barium sulfate and titanium dioxide. The weighed pellet can then be covered with a diffusion controlled membrane.

4. Low density (Floating) systems

Floating Drug Delivery Systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. These systems are suitable for drugs that are poorly soluble or unstable in the intestinal medium.

F) ELECTRICALLY STIMULATED RELEASE DEVICES[7]

These are monolithic devices prepared by using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile. Precise control over the release of drug from devices implanted in the body, such as quantity, timing, is highly desirable in order to optimize drug therapy. Electrically-controllable drug release from polyelectrolyte hydrogels is helpful in achieving these goals.

The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel complex erodes.

G) ION-EXCHANGE RESINS[7]

Ion exchange systems use resins composed of water insoluble cross linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$$Resin^{+}\ Drug^{--} + X^{--} \longrightarrow Resin^{+} - X^{--} + Drug^{--}$$

Conversely,

$$Resin^{---} - Drug^{+} + Y^{+} \longrightarrow Resin^{--} - Y^{+} + Drug^{+}$$

Where,

$X^-$and Y^+ are ions in the GI tract. The free drug then diffuses out of the resin. The drug-resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column or by prolonged contact in solution.

The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusional path length and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin. An improvement in this system is to coat the ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethylcellulose or wax. These systems rely on the polymer coat to govern the rate of drug availability.

Table No.5

A representative listing of ion-exchange resins is given below

Product	Active ingredient	Manufacturer
Biphetamine capsules	Amphetamine, Dextroamphetamine	Fisons
Ionamin capsules	Phenteramine	Pennwalt

1.6 ORAL CONTROLLED DRUG RELEASE POLYMERIC SYSTEMS[8]

For many years, the major focus of drug related research has been the synthesis or discovery of potent drugs with new kinds

of biological activity, which this continues to be an important area of research, increasing attention is being devoted to the manner in which these drugs are delivered. One way has been incorporation of drugs in solid polymers. Controlled release polymeric systems are the most promising as they increase efficacy of drugs substance and reduced undesirable side effects. The number of polymers and the range of formulation variables available to control the rates of drugs release from controlled release devices are broad. Selection among these variables is based upon the desired release rate and duration, the physical and chemical properties of the drug and the intended site of administration.

CHARACTERISTICS OF IDEAL POLYMERIC SYSTEM:

An ideal polymer system should possess the following characteristics:

- It should be inert and compatible with the environment.
- It should be non-toxic.
- It should be easily administered.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.

Criteria followed in polymer selection:

Polymer chosen as potential drug carrier must exhibit certain properties, as listed below:

- The polymer must be soluble and easy to synthesize, it must have a finite molecular weight and narrow distribution.

- It should provide drug attachment or release sites for the possibility of incorporation of drug –polymer linkages.
- The polymer should be compatible with the biological environment, i.e. non-toxic, non-antigenic and non-provocative in any other respect.
- It should be biodegradable or to be eliminated from the organism after the fulfillment of its function.

Types of polymers[9]

Polymers have been broadly classified as,

Natural polymers: These include acids, proteins, polysaccharides and complexes of proteins and polysaccharides.

Synthetic polymers: These include polyesters, polyurethane, polyamides, polycarbonates, polysiloxanes, polyolefins, polyvinyl compounds and acrylics.

Polymers can also be classified on the basis of their interaction with water, into non-biodegradable hydrophobic polymers.

1. Hydro gels.
2. Soluble polymers.
3. Biodegradable polymers.

Non-biodegradable polymers: These are inert in the environment of use, are eliminated or extracted intact from the site of administration and serve essentially as a rate-limiting barrier to the transport and release of drug from the device. Common examples of such materials includes polyethylene vinyl acetate (PVA), polydimethylsiloxane (PDS), polyurethane(PEU) ethyl cellulose, celluloseacetate, polyethylene, polyvinylchloride.

Hydro gels: These swell but not dissolve when brought in contact with water. They are inert, remove intact from the site of administration and function by forming a rate limiting barrier to the transport and release of drugs.

Common examples include ploy hydroxyethylmethylacrylate (p-HEMA), cross-linked polyvinyl alcohol, cross-linked polyvinyl pyrolidone, polyacrylamide and dextran.

Soluble polymers: These are moderate molecular weight uncross-linked polymers that dissolve in water. These materials can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time. Common examples include polyethylene glycol (PEG), polyvinylalcohol, Hydroxypropylmethylcellulose (HPMC) and copolymers of methacrylic acid.

Biodegradable polymers: These slowly disappear from the site of administration. However, this disappearance occurs in response to a chemical reaction such as hydrolysis. Common examples include polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL) and several generic classes such as polyanhydrides and polyorthoesters.[10]

LITERATURE REVIEW

LITERATURE REVIEW

- **Aiman A, et. al., (2000),** reported controlled release of Gabapentin from matrices using glyceryl benzoate[11]

- **Yagi Naomi, et. Al., (2000),** reported the compatibility of combining sustained release fine granules of nifedipine (SRN) with 32 kinds of drugs was studied of SRN and drugs in heat sealed packages (polyethylene laminated glassine paper) were kept at either 20°C and 75 % R.H. or 30 °C and 92% R.H. for 30 days.[12]

- **Shyamala Baskaran, et. al., (2002),** reported the novel approach to zero order drug delivery via hydro gel for diltiazem with HPMC followed by Higuchi pattern. Hydro gel matrix tablets of the drug were formulated using HPMC,SCMC with aim to attain a zero order release.[13]

- **Pandy, et. al., (2003),** reported formulation and release systems of sustained release of Diltiazem using HPMC at polymer ratio 1:60, using HPMC, ethyl cellulose and eudragit as a sustaining materials in various proportions. The hardness showed almost required result in the present study.[14]

- **Hajare, et. al., (2004),** reported a design of oral matrix formulation using guargum, NaCMC and HPMC. The data obtained were fitted into the Higuchi Model. Analysis of 'n' values of korsmeyer equation indicated that the drug release involved the diffusion.[15]

- **Srinath, et. al., (2004),** reported a complete study on the kinetics and mechanism of drug release from bilayer tablets of Diltiazem HCL. Matrix tablets of the drug were formulated using ethyl cellulose, rosin as matrix.[16]

- **Almeida S, et. al., (2006),** reported comparative study on the bio equivalence of two different Gabapentin formulations. A randomised, two periods, two sequence, crossover clinical trial in healthy volunteers.[17]

- **Supeecha Wittayalertpanya, et. al., (2008),** reported Bioequivalence study of two different formulations of 300 mg Gabapentin capsule in Thai healthy volunteers.[18]

- **Gorden A Irving, et. al., (2008),** reported tolerability and safety of gastrorententive once daily Gabapentin tablets for the treatment of post therapetic neuralgia.[19]

- **Gordi T, et. al., (2008),** reported Pharmacokinetics of gabapentin after a single day and at steady state following the administration of gastric-retentive-extended-release and immediate-release tablets: a randomized, open-label, multiple-dose, three-way crossover, exploratory study in healthy subjects[20]

- **Pfizer, (2009),** reported bioequivalence study of gabapentin between tablet and liquid formulation and the food effect study of liquid formulation.[21]

- **David Sandercock, et. al., (2009)** reported Gabapentin Extended Release for the Treatment of Painful Diabetic Peripheral Neuropathy.[22]

- **P M Ramdas Bhandarkar, et. al., (2009),** reported oxidative clavage of Gabapentin with N2 bromosuccinimide in acid medium.[23]

- **Wallace, et. al., (2010)** reported Gabapentin Extended-Release Tablets for the Treatment of Patients with Post herpetic Neuralgia: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study.[24]

- **Johns, et. al., (2010),** reported hydrophilic polymer viscosities on gastric retentive drug delivery systems of Gabapentin sustained release tablets[25]

- **Swati jagdale, et. al., (2010),** reported pharmaceutical equivalence of Gabapentin tablets with various extra granular binders.[26]
- **Cheng-hung Hsu, et. al., (2010)** reported progressive steps of polymorphic transformation of Gabapentin polymorphs studied by Hot stage FTIR microscopy.[27]
- **Abdollah Yari, et. al.,(2011),** reported Voltammetric Determination of Trace Antiepileptic Gabapentin with a Silver-Nanoparticle Modified Multiwalled Carbon Nanotube Paste Electrode[28]
- **Butch KuKanich, et, al., (2011),** reported Pharmacokinetics of oral Gabapentin in greyhound dogs.[29]
- **Zhixin Zong, et. al., (2011)** reported the Stabilizing Effect of Moisture on the Solid-State Degradation of Gabapentin.[30]
- **Ben Achrai, et. al., (2011)** reported Solubilization of Gabapentin into HII Mesophases.[31]
- **Ahmed N, et. al., (2011)** reported preparation and Invitro evaluation of floating microsphere of Gabapentin.[32]
- **Argoft CE, et. al., (2012),** reported clinical development of a once daily gastrorententive formulation of Gabapentin tablets for the treatment of post therapetic neuralgia.[33]
- **Yun-Seok Rhee, et. al., (2012), reported** Invivo/Invitro relationship of Gabapentin from a sustain release tablet formulation: A pharmacokinetic study in the Bengle dog.[34]

- **Swetha, et. al., (2012),** reported formulation and invitro evaluation of gastrorentive dosage form of Gabapentin.[35]

- **Cowels, et, al., (2012),** reported steady state pharmacokinetics of Gabapentin after administration of a novel gastrorentive Extended release formulation in postmenopausal women with vasomotor symptoms.[36]

- **Beal B, et. al.,(2012),** reported Gabapentin for once-daily treatment of post-herpetic neuralgia.[37]

- **James Tovera, et. al., (2012),** reported population pharmacokinetics and pharmacodynamics of gabapentin After Administration of Gabapentin Enacarbil.[38]

- **Dhanalakshmi P, et. al., (2012),** reported solid lipid nanoparticles hydrophyllic drug of Gabapentin for delivery of drugs to the brain.[39]

AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

In recent years, controlled release formulations have received considerable attention because of number of advantages that are offered in the field of pharmaceuticals. One of the applications of this technology is alteration of drug release profile with optimized effect.

Gabapentin is an anti-epileptic medication, also called an anticonvulsant. It affects chemicals and nerves in the body that are involved in the cause of seizures and some types of pain. It has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. The usual oral dosage regimen is 50-100mg every 4-6hrs with a maximum dosage of 400mg per day. To reduce the frequency of administration and to improve patient compliance a sustained release formulation of Gabapentin is desirable.

The aim of this work is to formulate and develop a novel oral controlled release tablet dosage form of Gabapentin to provide a steady state drug release over an extended period of time.

The rationale behind the mechanism and dynamics of electrolytes induced matrix stiffening and structural changes to the gel are the basis of controlled drug release.

The scope and objective behind this work is to prepare and evaluate Gabapentin tablets in order to control the drug release using different electrolytes in different concentrations.

PLAN OF WORK

4. PLAN OF WORK

The following experimental protocol was therefore designed to all systematic approach to the study.

1) Drug selection.

2) Selection of excipients.

3) Preformulation study: Compatibility evaluation was carried out between drug and polymers in physical observation and by using Infra Red spectrum study.

4) Formulation of controlled release matrix tablets of using different release retardant.

5) The following evaluation parameters were studied based on laboratory experiments.

i) In-process Evaluation of granules:

1. Angle of repose.
2. Apparent bulk density.
3. Tapped bulk density.
4. Percent compressibility.
5. Hausner Ratio.

ii) Evaluation of tablets:

i. Hardness.

ii. Friability.

iii. Weight variation.

iv. Content uniformity of active ingredient.

v. In-vitro dissolution study.

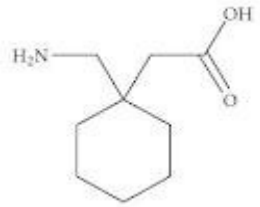
vi. Stability study of optimized batch.

DRUG PROFILE

5. DRUG PROFILE

Drug Profile of Gabapentin

Chemical Structure:



Chemical Name	**:**	2-[1-(aminomethyl)cyclohexyl]acetic acid
Molecular weight	**:**	171.237 g/mol
Molecular formula	**:**	$C_9H_{17}NO_2$
Physical properties		
Description	**:**	White to off white
Form	**:**	Crystalline solid
Category	**:**	Anticonvulsant, neuropathic pain and hot flashes.
Solubility	**:**	Freely soluble in water and acidic and basic solutions.
Storage	**:**	Store in the refrigerator
Melting Point	**:**	122 to 167°C.
Pka	**:**	3.7
Stability	**:**	91 days at 4°C, 56 days at 25°C.

Pharmacokinetics Profile:

Bioavailability	:	60% to 27%. (According to Dose increasing)
Biological half life	:	5 to 7 hrs.
Plasma protein binding	:	It is less than 3% bound to human serum proteins.
Excretion	:	Urinary excretion. 60% to 88% (unchanged drug and metabolites)

Pharmacodynamics Profile:

Mechanism of Action:

Gabapentin is structurally related to the neurotransmitter GABA (gamma-amino butyric acid) but it does not modify GABAA or GABAB radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

Gabapentin was formed by the addition of a cyclohexyl group to gamma-aminobutyric acid (GABA), which allowed this form of GABA to cross the blood-brain barrier.

Despite its structural similarity to GABA, Gabapentin does not bind to GABA receptors in the CNS. Its mechanism of action is unknown, but may involve enhanced neuronal GABA synthesis.

Pharmaco Kinetics:

Absorption and Bioavailability: It is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset.

Distribution: Less than 3% of gabapentin circulates bound to plasma protein.

Metabolism:

The pharmacokinetic profile of Gabapentin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, a number of pathways, including Cytochrome P-450 isozyme, CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Phase II hepatic metabolism renders the metabolites water-soluble, which are excreted by the kidneys. Thus, reduced doses may be used in renal and hepatic impairment.

Elimination:

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Contraindications:

Gabapentin controlled release tablets causes serious or fatal side-effects in a newborn including neonatal withdrawal syndrome, if the mother uses the medication during pregnancy or labor. Use of Gabapentin by nursing mothers is not recommended by the manufacturer because the drug passes into breast milk.

Dosage and Administration:

300-600 mg daily. Maintenance: 1200 mg daily (37-50 kg); 900 mg daily (26-36 kg).

Precaution:

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely

EXCIPIENTS PROFILE

6. EXCIPIENTS PROFILE

6.1 HYDROXY PROPYLMETHYL CELLULOSE[41]

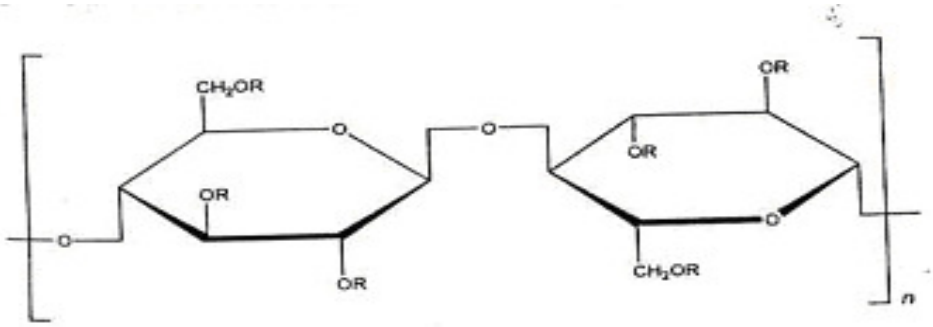
1 Synonym : Cellulose, E464, HPMC, methocel.

2 Chemical name : Cellulose, 2-hydroxy propyl methyl ether.

3 Empirical formula : (OCH_2CH (OH) CH_3)

4 Molecular weight : 1, 00, 00 to 1, 50, 00

5 Structural Formula :



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6. Functional category : Coating agent, film former, stabilizing agent, suspending agent, binding agent

7. Description : Odorless, tasteless, white or creamy white fibrous.

8. Typical Properties:

1. Bulk density : 0.341 g/cm

2. Tapped density : 0.557 g/cm

3. True density : 1.326 g/cm

4. Melting point : 190 to 200°C

5. P^H : 5.5 – 8.0

9. Solubility : Soluble in cold water, practically insoluble in ethanol, ether.

10. Stability and storage conditions : Its stable material, it's hygroscopic after drying. Stored in well-closed container. Protected from light

11. Incompatibilities : Incompatible with some oxidizing agents.

12. Safety: Nontoxic and nonirritant.

6.2 CALCIUM CARBONATE

1. **Molecular Formula**: $CaCO_3$.
2. **Molecular Weight**: 100.09.
3. **Functional category:** Buffering agent, Diluent, Therapeutic agent.
4. **Description:** Occurs as an odorless and tasteless, white powdered crystals.
5. **Applications:**

a. Employed as a pharmaceutical excipient.
b. Also used as a base for medicated dental preparations.
c. Used as bulking agent in tablet sugar coating processes.
d. Used as an opacifier in tablet film coating.
e. Used as a food additive.
f. Used as an antacid and calcium supplement.

6 .Typical Properties:

1. Bulk density -- 0.8 g/cm
2. Tapped density – 1.2 g/cm
3. Flow ability—cohesive.
4. Melting point – 825°C.

7. Solubility: Soluble in ethanol, water, insoluble in mineral oil and vegetable oil.

8. Stability and storage conditions: It's stable. Stored in well-closed container. Protected from light.

9. Safety: Nontoxic and Non- mucosal irritant.

6.3 MAGNESIUM CARBONATE

1. **Molecular formula:** $MgCO_3$.
2. **Molecular weight:** 84.32.
3. **Functional category:** Diluent, Antacid and Adsorbent.
4. **Applications:**
   a) As an excipient, it is mainly used as directly compressible tablet diluents.
   b) Also used in microsphere formulations.
   c) Used to absorb liquids, such as flavours in tableting process.

5. Description: Occurs as light, white colored friable masses or as bulky white powder.

6. Typical Properties:

1. Bulk density – 0.56 g/cm
2. Tapped density – 0.783 g/cm
3. Flow ability—Cohesive.
4. Melting point – 350°C.

7. Solubility: Soluble in water, insoluble in miner oil and vegetable oil.

8. Stability and storage conditions: It's stable. Stored in well-closed container. protected from light.

9. Safety: Nontoxic.

6.4 SODIUM BICARBONATE

1. Molecular formula: $NaHCO_3$.

2. Molecular weight: 84.01.

3. Functional category: Alkalizing agent and therapeutic agent.

4. Applications:

a) Employed as a source of carbon dioxide in effervescent tablets and granules.

b) Also used to buffer the drug molecules that are weak acids.

c) Also used as freeze-drying stabilizer.

5. Description: Occurs as an odorless, white crystalline powder.

6. Typical Properties:

1. Bulk density – 0.869 g/cm

2. Tapped density – 1.369 g/cm

3. Flow ability—Cohesive.

4. Melting point – 270°C.

7. Solubility: Soluble in water, insoluble in mineral oil and vegetable oil.

8. Stability and storage conditions: It's stable. Stored in well-closed container. Protected from light.

9. Safety: Nontoxic.

6.5 SODIUM CARBONATE

1. Molecular formula: Na_2CO_3.

2. Molecular weight: 105.99.

3. Functional category: Therapeutic agent.

4. Applications:

a) Employed as a food additive.

b) As a pharmaceutical excipient.

c) As an antacid.

5. Description: Occurs as white colored solid.

6. Typical Properties:

1. Bulk density – 2.5 g/cm
2. Flow ability—Cohesive.
3. Melting point –851°C.

7. Solubility: Soluble in water, insoluble in mineral oil and vegetable oil.

8. Stability and storage conditions: It's stable. Stored in well-closed container. Protected from light.

9. Safety: Non toxic.

MATERIALS AND METHODS

Table No. 6

7.1 MATERIALS

S.NO	INGREDIENTS	MANUFACTURER
1.	Gabapentin	Shasun Pharmaceuticals Ltd, Pondy.
2.	Methocel (HPMC)	Shasun Pharmaceuticals Ltd,. Pondy.
3.	Calcium carbonate	Shasun Pharmaceuticals Ltd, Pondy.
4.	Magnesium carbonate	Shasun Pharmaceuticals Ltd, Pondy.
5.	Sodium carbonate	Shasun Pharmaceuticals Ltd, Pondy.
6.	Sodium bicarbonate	Shasun Pharmaceuticals Ltd, Pondy.
7.	Talc	Shasun Pharmaceuticals Ltd, Pondy.

Table No .7

7.2 EQUIPMENTS

S. No	Name of the Equipment	Manufactured by
1.	8 stage dissolution apparatus	Electro lab, Ahmedabad.

2.	Tableting machine,(Mini Press-II MT)	Rimek 27 Stations, Ahemdabad.
3.	U.V/Visible spectrophotometer	Agilent, Japan.
4.	Analytical balance	Adair dutt Instruments
5.	Friabilator	VEEGO Instruments Corporation, Mumbai.
6.	Hardness tester	SQC& Inspection Instruments, Mumbai.
7.	Tray dryer	Pharmafab Industries,Hyd.
8.	Tapped density tester	Electrolab, Ahemdabad.
9.	Mechanical stirrer	Remimotor, Mumbai.

7.3 CALIBRATION CURVE OF GABAPENTIN

1. Preparation of 0.1N HCl

8.5 ml of concentrated hydrochloric acid was diluted up to 1000 ml with distilled water.

2. Preparation of Phosphate buffer pH 6.8

Accurately weighted quantity of 6.8 g of potassium dihydrogen phosphate and 0.89 gms of sodium hydroxide pellets were dissolved in distilled water and diluted with distilled water up to 1000 ml.

3. Preparation of standard curve in 0.1 N HCl

Accurately weigh one hundred mg of Gabapentin was taken in 100 ml volumetric flask and dissolved in 20 ml of methanol. Then the above solution was further diluted up to 100 ml with 0.1 N HCl. The resulting solution of 10 ml was taken and diluted up to 100ml to give a stock solution of 100 µg/ml with 0.1NHCl to get drug concentration 2,4,6,8,10,20,30,40,50 µg/ml. The absorbances of the solutions were measured against 0.1 N HCl (distilled water) as a blank at 270 nm using double beam UV visible spectrophotometer. The plot of absorbance v/s concentration (µg/ml) was plotted and data was subjected to weighed linear regression analysis in Microsoft excel.

Observation:

The standard calibration curve of drug in 0.1 N HCl depicted as Fig.2. The data of absorbance was shown in Table 8. The data had correlation coefficient of 0.9995 and the equation of regressed line depicted as eq.1

$$Y= 0.006 X + 0.0026, R^2= 0.9986.$$

4. Preparation of standard curve in 6.8 pH buffer

Accurately weigh one hundred mg of Gabapentin was dissolved in 100 ml volumetric flask and dissolved in 20ml of methanol. Then the above solution was further diluted up to 100ml with 6.8phosphate buffer. The resulting solution of 10ml was taken and diluted up to 100ml to give a stock solution of 100µg/ml with 6.8phosphate buffer to get drug concentration of 2,4 ,6,8 ,10,20, 30, 40, 50µg/ml. The absorbances of the solutions were measured against 6.8phosphate buffer as a blank at 270nm using double beam UV visible spectrophotometer. The plot of absorbance v/s concentration (µg/ml) was plotted and data was subjected to weighed linear regression analysis in Microsoft excel®

Observation

The standard calibration curve of drug in phosphate buffer pH 6.8 depicted as Fig.3. The data of absorbance was shown in Table 9. The data had correlation coefficient of 0.9993 and the equation of regressed line depicted as eq.3

$$Y= 0.006 X + 0.0042, R^2= 0.9963.$$

Table No.8

Calibration curve of Gabapentin in 0.1 N HCl at 270nm.

Sample No	Concentration (µg/ml)	Absorbance (nm)
1.	0	0
2.	2	0.010

3.	4	0.015
4.	6	0.029
5.	8	0.048
6.	10	0.057
7.	20	0.113
8.	30	0.187
9.	40	0.257
10.	50	0.295

Figure No.2

Calibration curve of Gabapentin with 0.1N Hcl at 270 nm

Y=0.006x

R^2=0.995

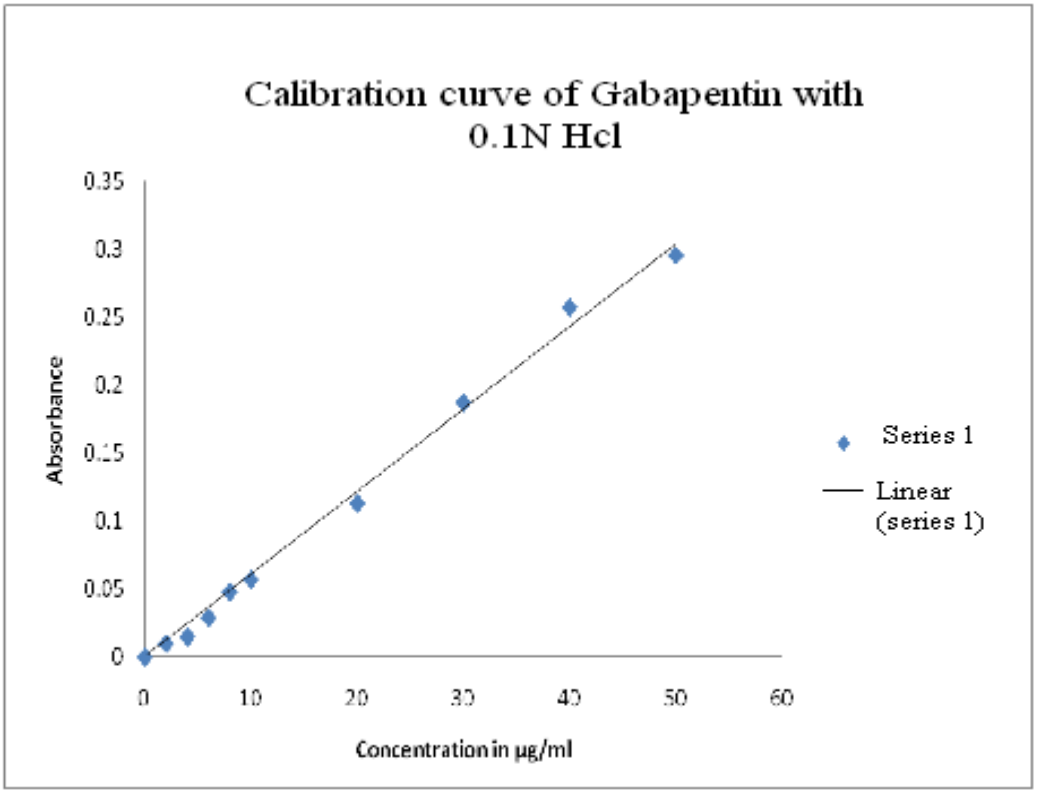


Table No.9

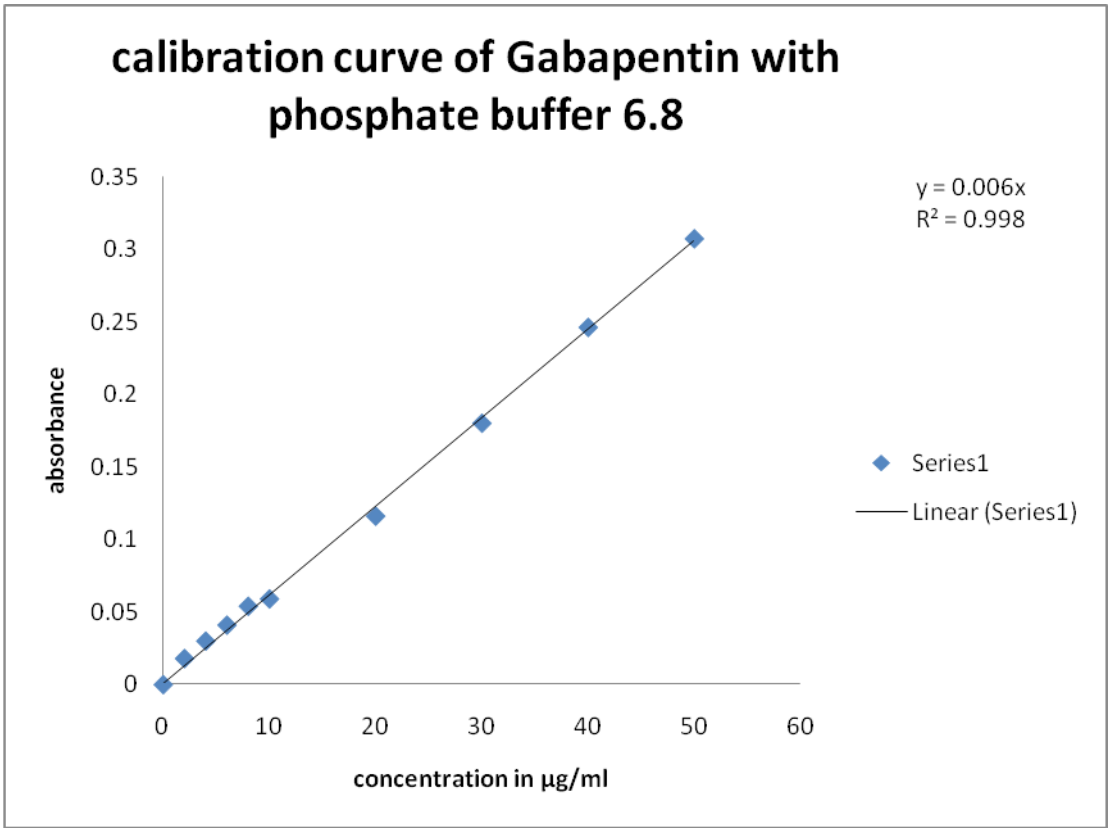
Calibration curve of Gabapentin with 6.8 phosphate buffer at 270nm.

Sample No	Concentration (µg/ml)	Absorbance (nm)
1.	0	0
2.	2	0.018
3.	4	0.030
4.	6	0.041
5.	8	0.054
6.	10	0.059
7.	20	0.116
8.	30	0.180

9.	40	0.246
10.	50	0.307

Figure No.3

Calibration curve of Gabapentin with 6.8 pH buffer at 270nm



7.4 IDENTIFICATION OF THE DRUG WITH I.R.SPECTRUM

The identification of drug was done by FT-IR spectroscopy. The FT-IR spectrum of pure drug Gabapentin is shown in Fig No. 4

Procedure:

Triturate 1-2mg of the drug substance to be examined with 300-400mg, unless otherwise specified of finely powdered and dried potassium bromide (or) potassium chloride. These quantities are usually sufficient to give a disc of 10- 15mm diameter and a spectrum of suitable intensity I.R spectrophotometers are used for recording spectra in the region of 4000- 650 cm-1

Figure. No.4

Identification of Gabapentin with I.R. Spectrum

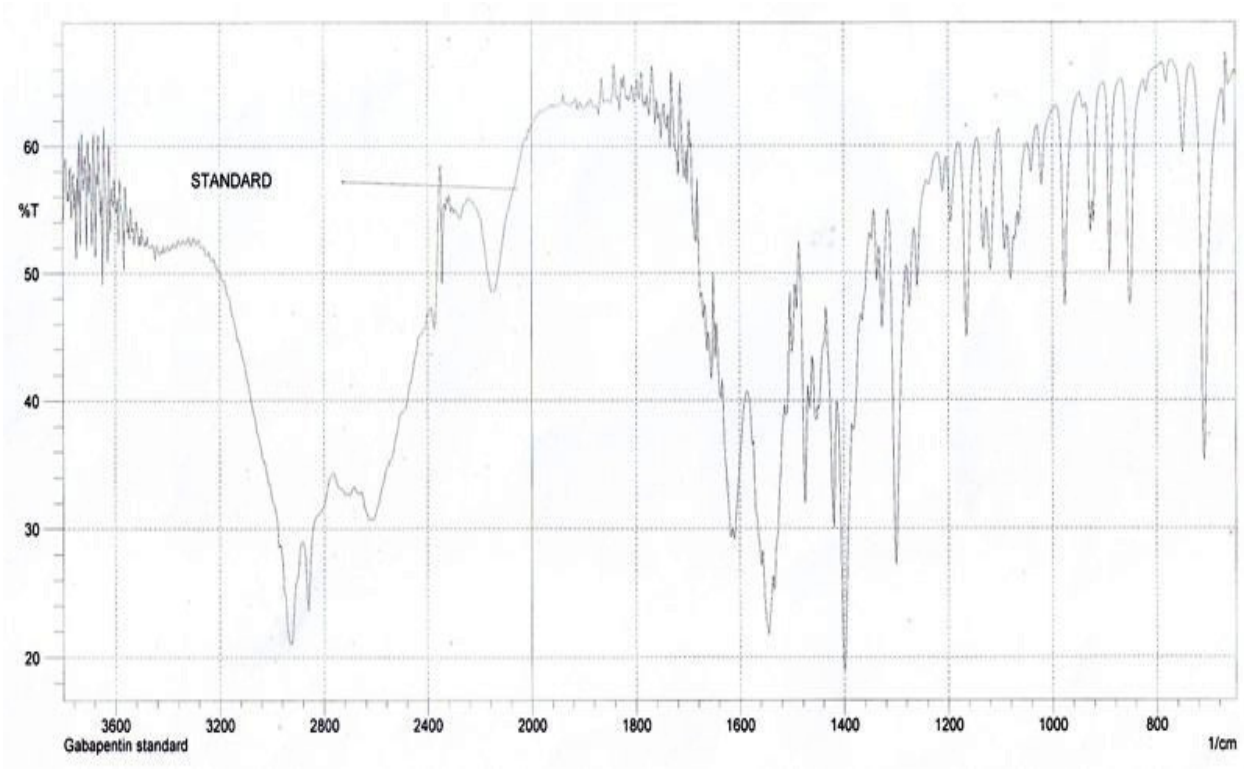


TABLE NO: 10

Identification of Gabapentin with I.R. Spectrum

S.NO	Wave number(cm-1)	Functional groups
1.	3475	N-H
2.	3450	O-H
3.	2950	C-H
4.	6575	C=O

7.5 DRUG AND EXCIPIENT COMPATABILITY STUDY:

In the drug and excipient compatability study, it was found that gabapentin is having compatibility with all the excipients used in the formulation. Active drug blended with individual excipients taken in 1:1 ratio. It was filled in closed vials and placed in stability chambers at 25 ± 2ºC at 55 ± 5 % RH and samples were observed for any physical changes at the end of 30 days, thus the chosen excipients for the formulations were found to be compatible with the active pharmaceutical ingredients also there was no change in the physical appearance of the blend.

TABLE NO: 11

Compatability studies of Drug with Excipients

S.No	Drug with Excipients	Initial colour	Storage conditions
			25°C/55%RH
			At the end 60 days
1.	D+HPMC	colourless	colourless
2.	D+$MgCO_3$	colourless	colourless
3.	D+$CaCO_3$	colourless	colourless
4.	D+$NaHCO_3$	colourless	colourless
5.	D+Na_2CO_3	colourless	colourless

PREFORMULATION STUDIES

8. PREFORMULATION STUDIES

1. BULK DENSITY:

It refers to a measurement to describe packing of particles. Bulk density issued to determine the amount of drug that occupies the volume in gm/cc.

$$Pi = m/Vi.$$

Where,

m =Mass of the blend.

Vi =Untapped volume.

Procedure:

Weigh the quantity of API and was transferred into a 100ml measuring cylinder without tapping during transfer. The volume occupied by the API was measured. Bulk density was measured by using formula.

2. TAPPED DENSITY:

Procedure:

Weigh the quantity of API and was taken into a graduate cylinder. Volume occupied by the API was noted down. Then the cylinder was subjected to 500, 750 and 1250 taps in tap density tester (Electro Lab USP II).According to USP ,the blend was subjected for 500taps.Percentage volume was calculated and subjected for additional 750 taps. Percentage variation is calculated.

$$Pt = m/Vt.$$

3. COMPRESSIBILITY INDEX:

Weigh the quantity of API and was transferred to 100ml graduated cylinder and subjected to 500, 750 and 1250 taps in tap density tester (Electro Lab).The difference between two taps should be less than 2%.The Percentage of compressibility index calculated using formula.

$$C.I = Vi\text{-}Vt/Vi \times 100.$$

LIMITS:

S.NO	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	> 40	Extremely poor

4. HAUSNER'S RATIO:

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5.It is determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = Vi/Vt.$$

Where,

Vi =Tapped volume.

Vt =Untapped volume.

LIMITS:

S.NO	Hausner's Ratio	Flow
1	1-1.2	Free flowing.
2	1.2-1.6	Cohesive powder.

5. ANGLE OF REPOSE:

Weigh the quantity of API and by using the methods of funnel type and open ended cylinderical methods, observe the height of the pile and the radius of the pile by placing the granules through it and the angle of repose can be measured by using formula,

$$[\text{Tan } \theta = h/r]$$

Where,

h = Height of pile.

r = Radius of the base of pile.

θ = Angle of repose.

Relation between Angle of Repose (a) and Powder flow:

S. No.	Angle of Repose	Flow
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable
4.	40 & above	Very poor

Table No.12

Preformulation Studies Results

S.No.	PARAMETERS	RESULTS
1.	Bulk density	0.32 -- 0.36 g/cc
2.	Tapped density	0.601 -- 0.609 g/cc
3.	Compressibility index	13 – 15%
4.	Hausner's ratio	1.12-- 1.16
5.	Particle size	26º34´--28º56´

9. FORMULATION OF GABAPENTIN TABLETS

The key process in the formulation development of Gabapentin. Tablets including direct compression method to be adopted using different excipients and before weighing active ingredient. The dispensing area maintained temperature below 25ºC and humidity below 30 % RH.

Procedure:

Accurately weigh the active (Gabapentin) and all other ingredients, were individually passed through sieve no.60 and then all the ingredients were mixed thoroughly by triturating upto 15 min.The mixed powder was lubricated with talc and the powder was again mixed thoroughly for punching to tablets by Direct compression method.

All the formulations were prepared according to the tables: 13, 14,15,16,17 the tablets were prepared as per the procedure given below and aim is to prolong the release of Gabapentin.

Table No.13

Composition of Gabapentin without electrolytes:

S.No.	Ingredients	Batch(F)
1.	Gabapentin	100mg
2.	HPMC 50cps	100mg
3.	Talc	3.25mg

Table No.14

Composition of Gabapentin Tablets using Calcium carbonate:

S.No.	Ingredients	F1	F2	F3	F4
1.	Gabapentin	100mg	100mg	100mg	100mg
2.	HPMC 50cps	100mg	100mg	100mg	100mg
3.	Calcium carbonate	25mg	50mg	75mg	100mg
4.	Talc	3.25mg	3.5mg	3.75mg	4.0mg

Table No.15

Composition of Gabapentin Tablets using Magnesium carbonate:

S.No.	Ingredients	F5	F6	F7	F8
1.	Gabapentin	100mg	100mg	100mg	100mg
2.	HPMC 50cps	100mg	100mg	100mg	100mg
3.	Magnesium carbonate	25mg	50mg	75mg	100mg
4.	Talc	3.25mg	3.5mg	3.75mg	4.0mg

Table No.16

Composition of Gabapentin Tablets using Sodium bicarbonate:

S.No.	Ingredients	F9	F10	F11	F12
1.	Gabapentin	100mg	100mg	100mg	100mg
2.	HPMC 50cps	100mg	100mg	100mg	100mg
3.	Sodium bicarbonate	25mg	50mg	75mg	100mg
4.	Talc	3.25mg	3.5mg	3.75mg	4.0mg

Table No.17

Composition of Gabapentin Tablets using Sodium carbonate:

S.No.	Ingredients	F13	F14	F15	F16
1.	Gabapentin	100mg	100mg	100mg	100mg
2.	HPMC 50cps	100mg	100mg	100mg	100mg
3.	Sodium carbonate	25mg	50mg	75mg	100mg
4.	Talc	3.25mg	3.5mg	3.75mg	4.0mg

EVALUATION STUDIES

10. EVALUATION STUDIES

The formulated tablets were evaluated for the following physicochemical parameters.

1. WEIGHT VARIATION TEST:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in table no.18, and none deviate by more than twice the percentage shown.

Table No.18

Weight variation tolerance for Tablet (USP)

S.No	Percentage Deviation allowed under Weight Variation test.	
	Average weight of tablet X mg	**Percentage deviation.**
1	X < 130 mg	10
2	130 < X < 324 mg	7.5
3	X < 324 mg	5

2. HARDNESS OF TABLET:

Hardness of the tablets was determined by using Digital Hardness Tester. Twenty tablets from each batch were randomly selected. The force required to break the tablet is recorded. The unit is Newton. The hardness of IP limits is NLT 5-8 kg/cm2.

The mean of measured hardness of tablets of each batch are shown in table no:19

3. FRIABILITY OF TABLET:

Friability of the tablets was tested using a Friabilator (Friability testing apparatus, Electro lab). A loss of less than 1& in weight was acceptable. The weight of 10 tablets was noted initially (W1) and placed in the friabilitor for 4 minutes/25 rpm. (Revolution per minutes). The tablets were reweighed and noted as (W2).

The difference in the weight is noted and expressed as percentage.

$$\text{Percentage friability (\%F)} = \frac{(W1 - W2)}{W1} \times 100$$

Where,

%F = Friability in percentage.

W1 = Initial weight of tablet.

W2 = Weight of tablets after revolution.

The mean of measured friability of tablets of each batch are shown in table no: 19

4. DRUG CONTENT: Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent weight of Gabapentin was transferred into 100ml volumetric flask and by using methanol as the extracting solvent and the samples was analyzed by spectrophotometrically.The results are listed in table no.19

Table No.19

PHYSICAL PARAMETERS OF GABAPENTIN TABLETS

B. No.	Average Weight (mg)	Hardness (kg)	Friability (%)	Percentage drug content (%)
F1	321±1.35	5.2±0.02	0.840	99.50
F2	323±1.82	5.1±0.03	0.812	100.3
F3	329±2.45	5.5±0.04	0.840	100.1
F4	334±3.75	5.7±0.02	0.831	99.8
F5	324±1.62	5.2±0.05	0.811	99.65
F6	325±2.53	5.5±0.03	0.652	99.95
F7	328±2.75	5.6±0.02	0.725	100.4
F8	336±2.98	5.1±0.04	0.845	100.1
F9	327±1.28	5.2±0.03	0.832	100.2
F10	329±1.55	5.4±0.01	0.840	99.9
F11	333±2.78	5.2±0.03	0.821	99.89
F12	335±2.04	5.5±0.02	0.832	100.1
F13	328±2.82	5.2±0.05	0.795	100.2
F14	332±2.53	5.3±0.03	0.823	100.2
F15	334±2.73	5.4±0.04	0.822	99.98
F16	337±3.04	5.7±0.01	0.755	99.95

5. IN VITRO DISSOLUTION STUDIES OF TABLETS

Dissolution parameters:

- Apparatus – USP-II.
- Dissolution medium – 0-2hrs (0.1HCl)
  3-12hrs (6.8 phosphate buffer)
- RPM-----50.
- Sampling Interval-----1,2,3,4,5,6,7,8,9,10,11,12hrs.
- Temperature---------37 ±0.5ºc.

Dissolution study:

As the preparation was for prolonged release given through oral route of administration, different receptor fluids are used for evaluation of the dissolution profile.

Procedure: 900ml of 0.1HCl solution was placed in the vessel and the USP —II apparatus (paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37±0.5ºc.The tablets of each batch were placed in the vessels and the vessels are covered. The apparatus was operated for 2hrs and the medium Phosphate buffer 6.8 was taken for the continued process from 3-12hrs at 50 rpm. At a definite time intervals of 5ml of the receptor fluid was withdrawn, filtered again 5ml of receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 270nm using U.V-Spectrophotometer.

6. DRUG RELEASE KINETICS - MODEL FITTING OF THE DISSOLUTION DATA DRUG RELEASE KINETICS

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f (t). Some analytical definitions of the Q (t) function are commonly used, such as Zero order, First order, and Higuchi and Korsmeyer–Peppas models.

Table No.20

DRUG RELEASE KINETICS

Kinetic Model	Relation	Systems Following the Model
First order	$\ln Q_t = \ln Q_o + K_t$ (release is proportional to amount of drug remaining)	Water-soluble drugs in porous matrix
Zero order	$f_t = K_o t$ (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	$f_t = K_H t^{1/2}$ (proportional to square root of time)	Matrix formulations
Peppas – Korsemeyer $M_t / M_\alpha = K_s t^2$	Erodible isometric matrices	f_t = Fraction of dose released at time‘t’; K_H, K_o, and K_s = release rate constants characteristic to respective models; Q_o = The drug amount

		remaining to be released at zero hour; Q_t = The drug amount remaining to be released at time 't'; M_t = Initial amount of drug present in the matrix at time't', M_α = Amount of drug released at time 'α'.

7. MECHANISMS OF DRUG RELEASE

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in Korsmeyer–Peppas model which is often used to describe the drug release behaviour from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved.

$$\text{Log } (M_t / M_\infty) = \text{Log } K_{KP} + n \text{ Log } t$$

Where,

M_t is the amount of drug release at time t,

M_∞ is the amount of drug release after infinite time;

K_{KP} is a release rate constant incorporating structural and geometrical characteristics of the tablet, and n is the release exponent indicative of the mechanism of drug release.

Table No.21

Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

TABLE NO.22

COEFFICIENT CORRELATION (R) VALUES FROM IN VITRO DISSOLUTION RATES OF GABAPENTIN TABLETS

Batch N0.	Zero Order	First Order	Higuchi's	Peppas's
F1	0.98740	0.9630	0.9848	0.9367
F2	0.9907	0.9601	0.9822	0.9211
F3	0.9944	0.9889	0.9769	0.9301
F4	0.9957	0.9901	0.9751	0.9342
F5	0.9943	0.9829	0.9788	0.9380
F6	0.9959	0.9830	0.9736	0.9369

F7	0.9618	0.9838	0.9690	0.9336
F8	0.9975	0.9909	0.9668	0.9801
F9	0.9890	0.9902	0.9851	0.9348
F10	0.9925	0.9913	0.9828	0.9345
F11	0.9940	0.9934	0.9798	0.9349
F12	0.9970	0.9824	0.9748	0.9318
F13	0.9942	0.9886	0.9796	0.9324
F14	0.9955	0.9792	0.9786	0.9320
F15	0.9967	0.9734	0.9721	0.9332
F16	0.9975	0.9701	0.9648	0.9341

TABLE NO.23

DISSOLUTION PROFILE OF GABAPENTIN TABLETS PREPARED WITH CALCIUM CARBONATE IN DIFFERENT CONCENTRATIONS [F1, F2, F3, and F4]. F-WITHOUT ANY ELECTROLYTES.

TIME (hrs)	CUMULATIVE PERCENTAGE DRUG RELEASE				
	F	F1	F2	F3	F4
1.	36.07	21.20	19.27	16.20	15.78
2.	53.95	34.25	32.07	28.23	25.19
3.	66.32	42.06	37.47	34.11	32.08
4.	81.59	47.05	45.61	42.43	40.11
5.	90.95	53.96	50.23	46.89	45.24
6.	98.92	61.38	59.80	56.99	55.26
7.	101.50	67.30	66.15	63.62	60.22

8.	97.54	70.84	68.94	66.06	64.62
9.	96.14	80.04	78.74	76.33	74.61
10.	95.88	89.31	87.99	85.14	83.76
11.	93.17	90.28	91.21	93.17	90.79
12.	90.79	95.57	92.37	96.26	93.04

Figure No.5

Dissolution profile of Gabapentin with Calcium Carbonate.

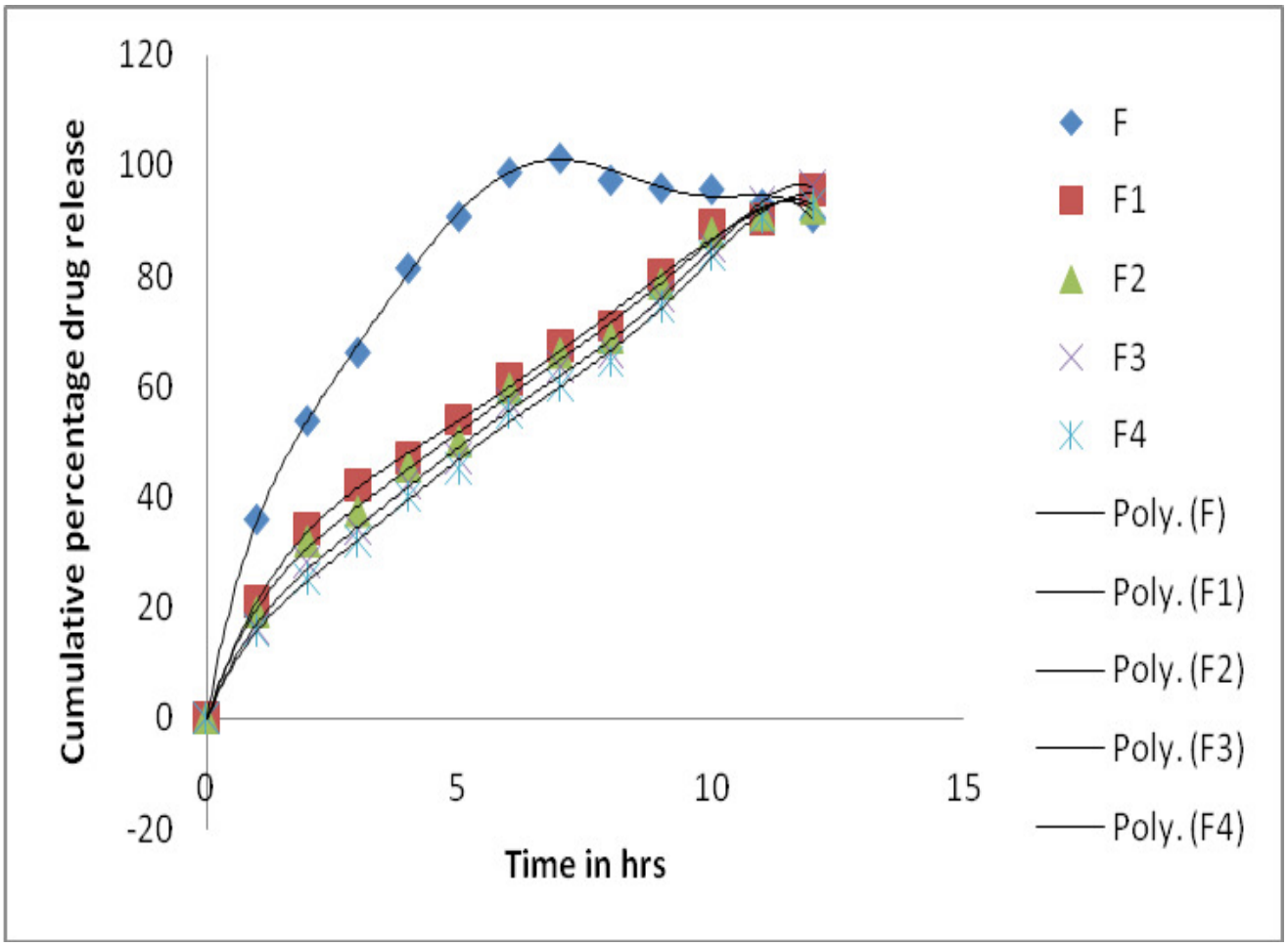


TABLE NO.24

DISSOLUTION PROFILE OF GABAPENTIN TABLETS PREPARED WITH MAGNESIUM CARBONATE IN DIFFERENT CONCENTRATIONS [F5, F6, F7, F8].F-WITHOUT ANY ELECTROLYTES.

TIME (hrs)	CUMULATIVE PERCENTAGE DRUG RELEASE				
	F	F5	F6	F7	F8
1.	36.07	17.36	14.35	11.11	09.63
2.	53.95	25.58	23.10	22.32	20.10
3.	66.32	35.74	32.99	29.39	27.09
4.	81.59	41.23	38.26	36.99	33.25
5.	90.95	46.93	44.28	42.07	40.58
6.	98.92	53.64	52.92	50.45	48.50
7.	101.50	60.39	58.33	56.38	54.36
8.	97.54	66.35	63.28	62.04	60.11
9.	96.14	73.58	70.87	69.54	68.75
10.	95.88	81.56	79.94	78.56	73.56
11.	93.17	89.12	88.01	86.25	82.69
12.	90.79	92.65	93.27	95.05	94.12

Dissolution profile of Gabapentin with Magnesium Carbonate.

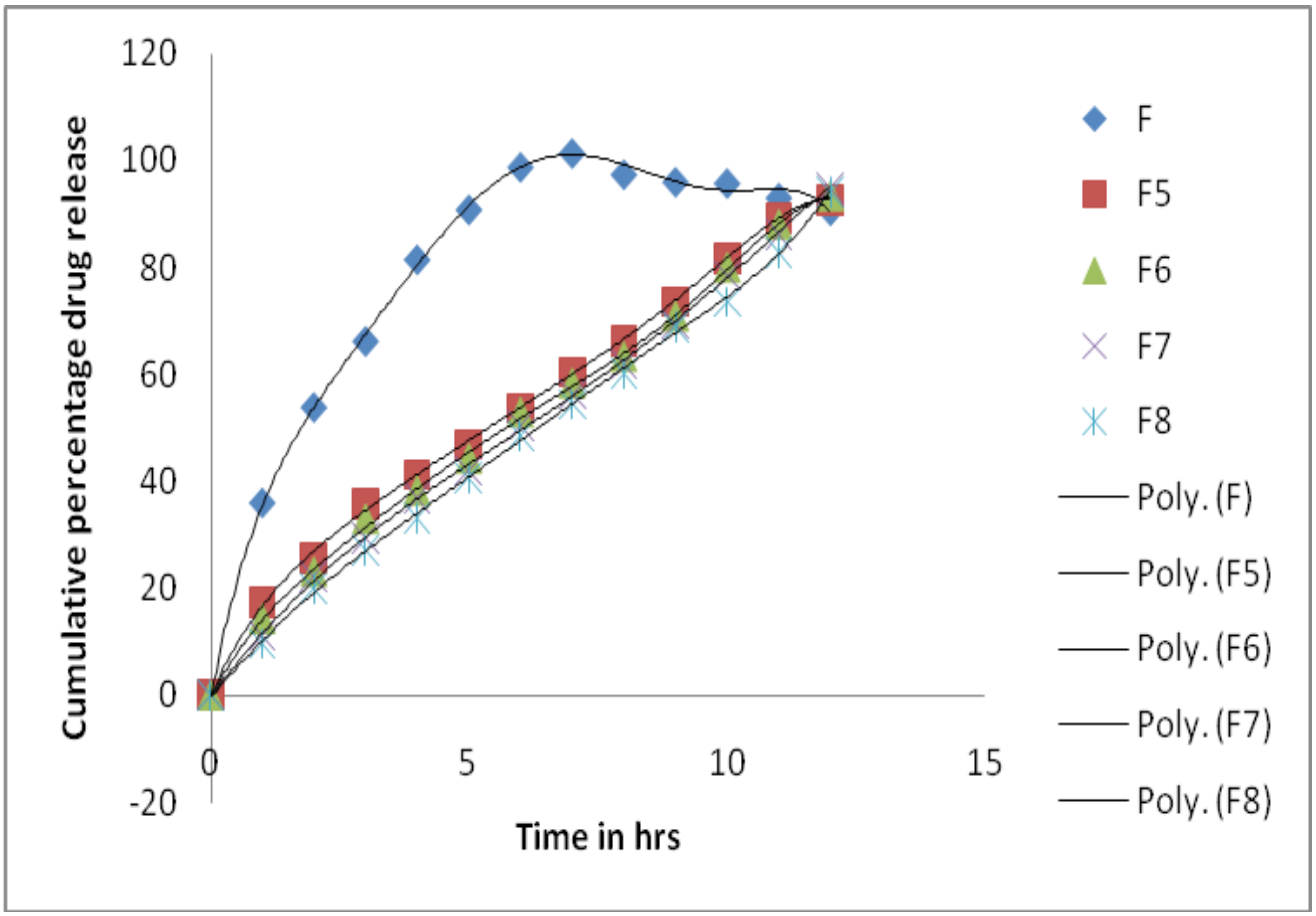

120
100
80
60
40
20
0
-20
0
5
10
15
Cumulative percentage drug release
Time in hrs
F
F5
F6
F7
F8
Poly. (F)
Poly. (F5)
Poly. (F6)
Poly. (F7)
Poly. (F8)

TABLE NO.25

DISSOLUTION PROFILE OF GABAPENTIN TABLETS PREPARED WITH SODIUM BICARBONATE IN DIFFERENT CONCENTRATIONS [F9, F10, F11, F12].F-WITHOUT ANY ELECTROLYTES.

TIME (hrs)	CUMULATIVE PERCENTAGE DRUG RELEASE				
	F	F9	F10	F11	F12
1.	36.07	24.15	22.65	20.45	17.35
2.	53.95	29.27	28.15	26.18	24.00
3.	66.32	39.67	37.69	35.08	31.65
4.	81.59	47.72	45.92	43.66	39.65
5.	90.95	55.36	51.58	48.36	46.28
6.	98.92	59.65	58.73	56.92	53.79
7.	101.50	69.35	66.81	64.36	61.59
8.	97.54	71.12	72.41	70.63	69.17
9.	96.14	79.61	78.74	75.68	75.50
10.	95.88	88.07	87.20	85.40	82.36
11.	93.17	92.49	94.63	93.55	92.57
12.	90.79	94.68	96.73	95.36	96.15

Dissolution profile of Gabapentin with Sodium Bicarbonate.

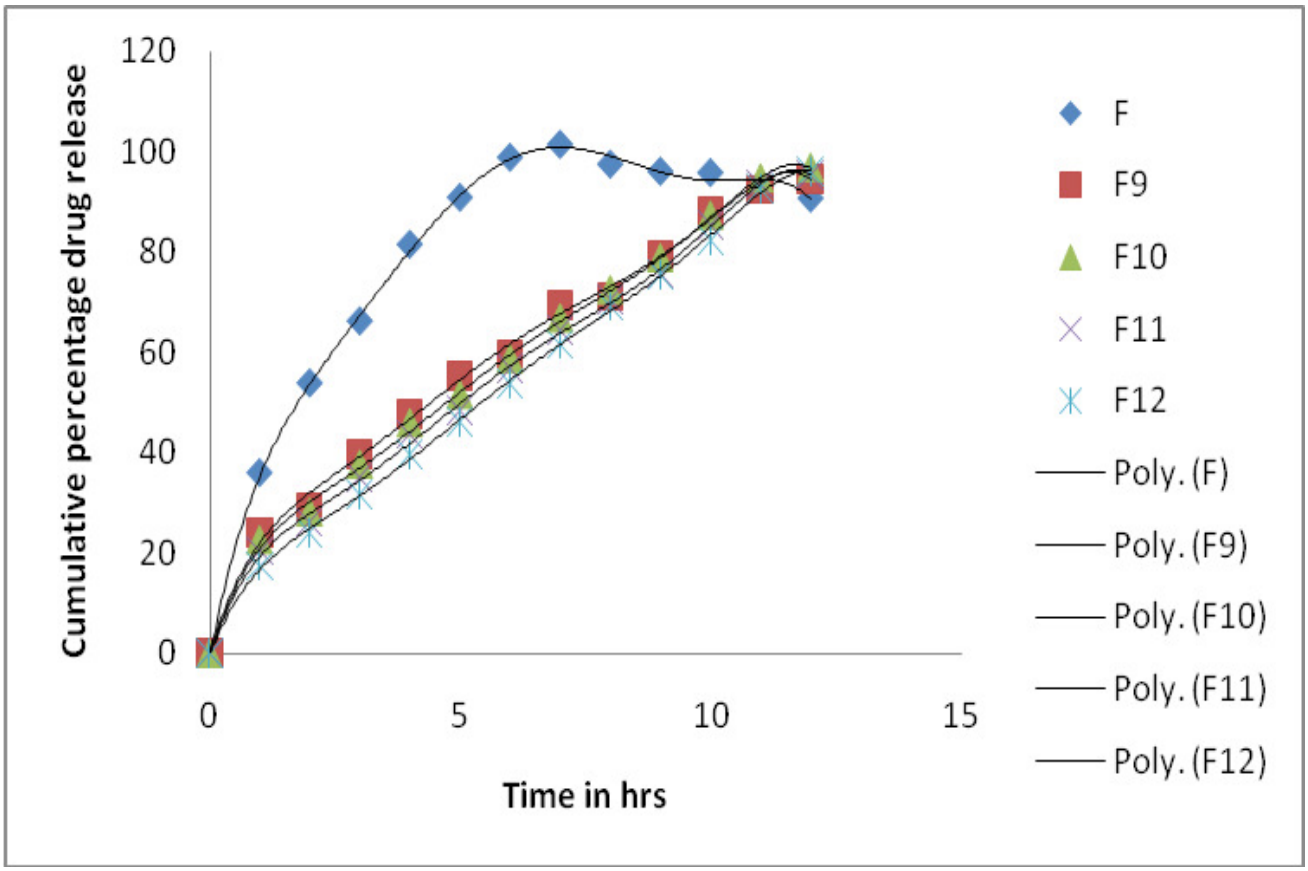


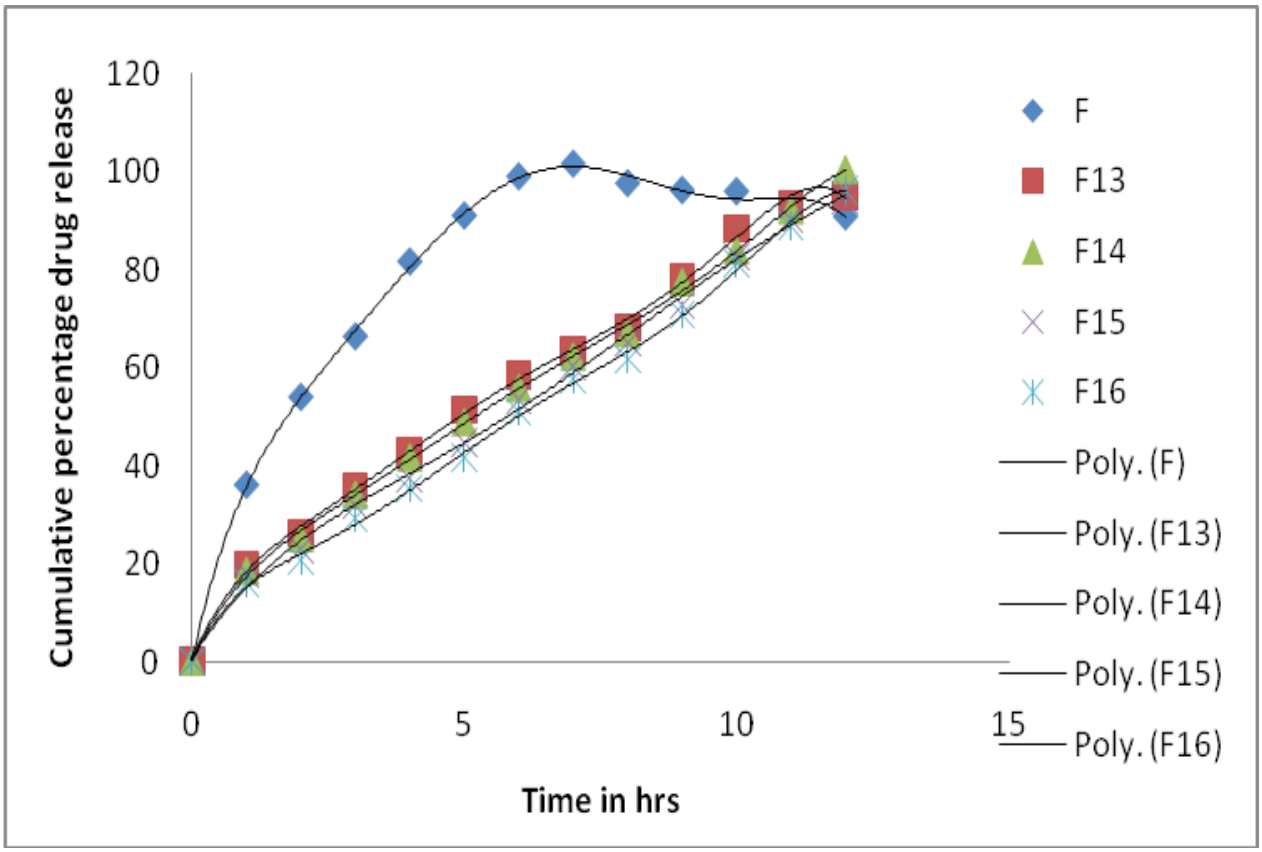
TABLE NO.26

DISSOLUTION PROFILE OF GABAPENTIN TABLETS PREPARED WITH SODIUM CARBONATE IN DIFFERENT CONCENTRATIONS [f13, f14, f15, f16].f-WITHOUT ANY ELECTROLYTES

TIME (hrs)	CUMULATIVE PERCENTAGE DRUG RELEASE				
	F	F13	F14	F15	F16
1.	36.07	19.64	18.54	17.98	16.15
2.	53.95	26.18	25.24	23.08	20.78
3.	66.32	35.45	34.14	31.99	29.24
4.	81.59	42.70	41.75	37.40	35.36
5.	90.95	51.32	48.96	44.74	41.81
6.	98.92	58.36	55.93	53.42	51.11
7.	101.50	63.28	62.30	60.42	57.84
8.	97.54	68.02	67.12	65.08	61.85
9.	96.14	78.36	77.54	72.74	70.87
10.	95.88	88.36	84.01	82.74	81.36
11.	93.17	93.29	92.25	90.43	89.12
12.	90.79	95.03	100.53	94.45	96.43

Figure No.8

Dissolution profile of Gabapentin with Sodium Carbonate.


Cumulative percentage drug release
120
100
80
60
40
20
0
0
5
10
15
Time in hrs
F
F13
F14
F15
F16
Poly. (F)
Poly. (F13)
Poly. (F14)
Poly. (F15)
Poly. (F16)

STABILITY STUDIES

11. STABILITY STUDIES OF THE OPTIMIZED BATCH

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product is not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted.

The International Conference on Harmonization (ICH) Guidelines titled stability testing of new drug substances and product describes the stability test requirements for drug registration application in the European Union, Japan and United states of America. ICH specifies the length of study and storage conditions.

Long term testing : 25 ˚C ± 2 ˚ C and 60 % ± 5 % RH for 24 months.
Accelerated testing: 40 ˚ C ± 2 ˚ C and 75 % ± 5 % RH for 6 months.

Stability studies work for present work carried out at controlled room temperature. i.e. Long term studies at 25 ˚C ± 2 ˚ C and 60 % ± 5 % RH for 3 months.

For any Extended or Controlled release formulations containing the water swellable polymers like HPMC, at high temperatures de-Polymerization take place. So their stability studies will carry out at long term studies.

Method:

The selected blister packed formulations stored at 25˚C ± 2 ˚ C and 60 % ± 5 % RH for 12 weeks and evaluated for their physical appearance and drug content at specified intervals of time. The formulations were further scanned to observe any possible spectral changes and also performed in-*vitro* dissolution studies. The results are tabulated in table no.27

TABLE NO.27

STABILITY DATAS

Specification (Limits)	**Initial**	**1 Month**	**2 Months**
Description	Complies	Complies	Complies
Average Weight (330 ± 10 mg)	332	334	334
Hardness NLT (5.0K.g/cm^2)	5.3	5.4	5.2
Dissolution of Best Batch (F14)	**1st** -- 18.94 **6th** -- 55.34 **12th** -- 100.53	**1st** -- 17.41 **6th** -- 54.12 **12th** -- 99.72	**1st** -- 17.12 **6th** -- 52.11 **12th** -- 98.14
Assay (99.9- 100.9 %)	100.2	99.96	99.93

RESULTS AND DISCUSSION

12. RESULTS AND DISCUSSION

The present study was under taken to evaluate and to design the controlled release matrix tablet of Gabapentin with HPMC by employing electrolytes as rate retardants. All the batches were evaluated for physical parameters and also for the in vitro evaluation studies.

The results show various dissolution parameters computed for all the controlled release formulations. The total Gabapentin drug release was about 100.57% indicating almost the complete drug release from the formulation of F14 with the electrolyte as sodium carbonate.

The inclusion of the electrolyte with in the swollen matrix for controlling the release rate of Gabapentin might lead to the formulation of free base of drug and fundamental structure change in gel boundary, thus indicating the textual variation in swollen matrix. The mechanism may prevail during the period of drug release from the swollen gel structure. As the dissolution medium enters the tablet, there is a rapid electrolyte water interaction with significant chemical reaction. From these changes and alterations the mechanism of intragel is possible to inhibit the drug release rate.

The stability studies were performed on selected formulation i.e., F14 at 25±2˚C and 60±5%RH at the interval of 2 months .The formulation were checked for physical appearance, drug content, hardness and dissolution. There was no physical change has been observed in the formulation at all and also there was no significant change has been observed in drug content, hardness and dissolution of the selected formulation and the specific conditions. So F14 formulation were found to be stable.

CONCLUSION

13. CONCLUSION

From the above results and discussion it was concluded that electrolytes can be used as aids to controlled drug delivery in the formulation of water soluble drugs from the tablet matrix.

The release rate of drug from the matrix tablets can be governed by the polymer and concentration of the electrolytes employed in the preparation of tablets.

The electrolyte of sodium carbonate was more effective release rate retardants than the other electrolytes. The optimal batch formulation F14 which showed an optimal release pattern up to 12hrs. The batch formulation F14 of sodium carbonate at an optimal concentration is effective and can be administered twice daily.

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